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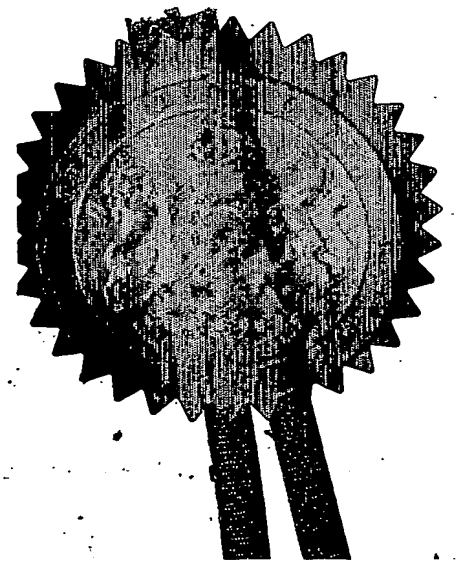

Signed Andrew Cray

Dated 26 March 2004

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1/77

Request for grant of a patent

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12 MAY 2003

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1.	Your reference	4-33177P1	13MAY03 E806598-1 000524 P01/7700 0.00-0310867.7
2.	Patent application number *(The Patent Office will fill in this*	0310867.7	
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND 7125487005	
4.	Title of invention	Organic Compounds	
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH 1800001	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
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7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes	

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co. — Date: 12th May 2003

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr
020 8560 5847

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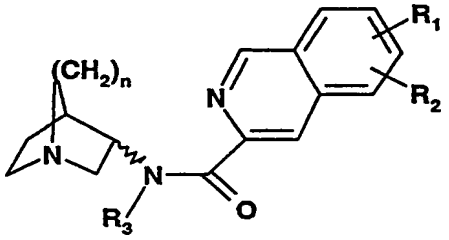
DUPLICATE

Organic Compounds

The present invention relates to novel isoquinoline-3-carboxylic acid amides having α7 nicotinic acetylcholine receptor agonistic activity, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides a compound of formula I



I

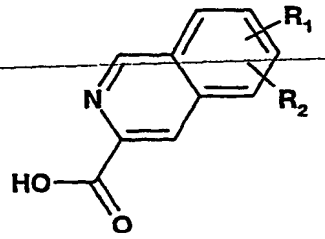
wherein R_1 and R_2, independently, are hydrogen, (C_{1-4})alkyl, halogen, hydroxy, (C_{1-4})alkoxy, di(C_{1-4})alkylamino, (C_{1-4})alkylthio, cyano or trifluoromethyl, R_3 is hydrogen or (C_{1-4})alkyl and n is 1 or 2, in free base or acid addition salt form.

Halogen denotes fluorine, bromine, chlorine or iodine.

Any alkyl, alkoxy or alkylthio groups are branched or straight chain groups. They are preferably methyl, methoxy or methylthio groups. n is preferably 2.

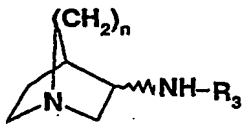
On account of the asymmetrical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the step or reacting a compound of formula II



II

wherein R_1 and R_2 are as defined above, with a compound of formula III



III

wherein R_3 and n are as defined above, and recovering the resulting compound of formula I in free base or acid addition salt form.

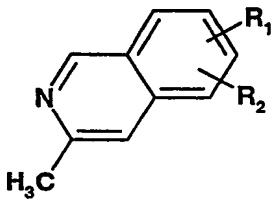
The reaction can be effected according to conventional methods, e.g. as described in the examples.

Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

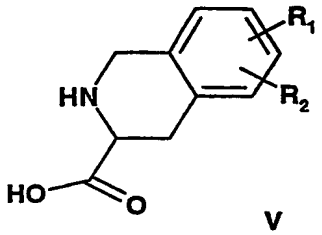
Acid addition salts may be produced from the free bases in known manner, and vice versa.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures. Alternatively, optically pure starting materials can be used.

The starting compounds of formula II may be obtained by conventional methods e.g. by oxidation of compounds of formula IV or V



IV



V

wherein R_1 and R_2 are as defined above, according to conventional methods.

The starting materials of formula III, IV and V are known or may be obtained from known compounds, e.g. as described in the Examples.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In particular, the agents of the invention are α7 nicotinic acetylcholine receptor (nAChR) agonists.

In functional assays, the agents of the invention display high affinity at the α7 nAChR as shown in the following tests:

a) A functional assay for affinity at α7 nAChR is carried out with a rat pituitary cell line stably expressing the α7 nAChR. As a read out, the calcium influx upon stimulation of the receptor is used. In this assay, agents of the invention exhibit pEC_{50} values of about 5 to about 8.

b) To assess the selectivity of the agents of the invention, a similar functional assay is carried out using a human epithelial cell line stably expressing the neuronal α4β2 nAChR subtype. In this assay, agents of the invention display no or little activity at the α4β2 nAChR.

c) To assess the selectivity of the compounds of the invention, similar functional assays as described under a) are carried out with a human epithelial cell line stably expressing the

ganglionic nACHR subtype or a cell line endogenously expressing the muscle type of nicotinic receptors. In these assays, agents of the invention display no or little activity on the ganglionic and muscle type of nicotinic receptor subtypes.

In the model of mice showing sensory gating deficit (DBA/2-mice) described by S. Leonard et al. in Schizophrenia Bulletin 22, 431-445 (1996), the agents of the invention induce significant sensory gating at concentrations of about 10 to about 40 μM.

The agents of the invention are therefore useful for the treatment of psychotic disorders such as schizophrenia, mania, depression and anxiety, and for the treatment of neurodegenerative disorders such as senile dementia, Alzheimer's disease and other intellectual impairment disorders, such as attention deficit hyperactivity disorders (ADHD), cognitive dysfunctions and memory deficits; Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, furthermore for the treatment of pain, epilepsy and inflammatory disorders such as rheumatoid arthritis and Crohn's disease. The usefulness in inflammatory disorders is based on the finding that α-7 agonists reduce TNF release from macrophages, as reported in Wang et al., Nature,2002:421, 384. The usefulness of α7 nAChR agonists in neurodegeneration is also documented in the literature, e.g. in Wang et al., J. biol. Chem. 275, 5626-5632 (2000).

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.01 to about 100, preferably from about 0.1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 5 to about 300 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of any condition mentioned above.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from about 1 to about 25 mg of a compound according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Example 1: Isoquinoline-3-carboxylic acid {(S)-1-azabicyclo[2.2.2]oct-2-yl}-amide

529 mg of isoquinoline-3-carboxylic acid hydrate are dissolved in 18 ml of DMF, followed by addition of 508 mg of 1-hydroxy-benzotriazol and 1.81 g of dicyclohexyl-carbodiimide. After stirring for 1 h at r.t., the precipitated dicylohexyl-urea is filtered off and 500 mg of 3(S)-aminoquinuclidine dihydrochloride and 1.3 ml of ethyl-diisopropylamine is added to the filtrate. After stirring for 48 h at room temperature, a second portion of dicylohexyl-urea is filtered off and washed with MeOtBu/DMF (4:1). Wash solution and filtrate are combined and crystallized by standing over night at 5°. The crystalline precipitate is filtered off and washed with MeOtBu/DMF (4:1), followed by MeOtBu to yield the title compound as monohydrochloride.

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.75 (1H, t), 1.96 (2H, m), 2.12 (1H, q), 2.24 (1H, d), 3.24 (3H, m), 3.43 (2H, m), 3.65 (1H, t), 4.49 (1H, q), 7.86 (1H, t), 7.92 (1H, t), 8.24 (1H, d), 8.30 (1H, d), 8.61 (1H, s), 9.31 (1H, d), 9.46 (1H, s), 10.59 (1H, br).
MS (ES^+): 282 $(MH)^+$

Example 2: Isoquinoline-3-carboxylic acid {(R)-1-azabicyclo[2.2.2]oct-2-yl}-amide

The compound is prepared as monohydrochloride according to Example 1 starting from 3(R)-aminoquinuclidine and isoquinoline-3-carboxylic acid hydrate.

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.76 (1H, t), 1.96 (2H, q), 2.12 (1H, q), 2.24 (1H, d), 3.22 (3H, m), 3.45 (2H, m), 3.64 (1H, t), 4.49 (1H, q), 7.88 (1H, t), 7.96 (1H, t), 8.25 (1H, d), 8.33 (1H, d), 8.71 (1H, s), 9.38 (1H, d), 9.49 (1H, s), 10.77 (1H, s).
MS (ES^+): 282 $(MH)^+$

Example 3: 6-Fluoro-isoquinoline-3-carboxylic acid {(R)-1-azabicyclo[2.2.2]oct-2-yl}-amide

The compound is prepared according to Example 1 starting from 3(R)-aminoquinuclidine and 6-fluoro-isoquinoline-3-carboxylic acid. Further purification is achieved by chromatography on silica gel eluting with MeOtBu/EtOH/conc. aqu. NH_3 (75/22.5/2.5).

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.38 (1H, m), 1.63 (2H, dt), 1.78 (1H, m), 1.93 (1H, q), 2.65-2.80 (4H, m), 2.94 (1H, dt), 3.18 (1H, dt), 4.06 (1H, m), 7.72 (1H, dt), 8.04 (1H, dd), 8.39 (1H, q), 8.57 (1H, s), 8.76 (1H, d), 9.42 (1H, s).
MS (ES$^+$): 300 $(MH)^+$

The starting material can be prepared as follows:

6-Fluoro-isoquinoline-3-carboxylic acid hydrochloride

2.15 g of 6-fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester are dissolved in 120 ml of xylene. 1.6 g of Pd-C (10%) is added and the suspension is refluxed during 8 h. The catalyst is filtered off, washed with MeOH and the filtrate, combined with the wash solution, evaporated to dryness.
1 g of the resulting crude 6-fluoro-isoquinoline-3-carboxylic acid methyl ester is dissolved in 20 ml of MeOH/THF (1:1) and slowly mixed at 5° with a solution of 510 mg of LiOH hydrate in 10 ml of water. The resulting solution is stirred at room temperature overnight and poured into a solution consisting of 50 ml of MeOtBu, 10 ml of water and 7 ml of 2N aqu. HCl. The precipitate is filtered off and washed with MeOtBu.

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 7.77 (1H, dt), 8.04 (1H, dd), 8.38 (1H, dt), 8.66 (1H, s), 9.43 (1H, s).
MS (ES$^-$): 190 $(M-H)^-$

6-Fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester

2 g of m-fluoro-DL-phenylalanine are suspended in 20 ml of conc. hydrochloric acid and 8 ml of aqu. 37% formaldehyde solution and stirred during 3.5 h at 90° during which a partial solution takes place. Stirring is continued overnight at room temperature and the precipitate filtered off and washed with cold water. Filtrate, combined with the wash solutions are evaporated to dryness, the residue suspended in 50 ml of MeOH saturated with HCl and stirred overnight, during which a clear solution is formed. The solvent is evaporated, the residue dissolved in CH_2Cl_2/MeOH (9:1) and extracted with 2N Na_2CO_3 solution and brine. The organic phases are dried over Na_2SO_4, evaporated and chromatographed on silica gel using MeOtBu. The title compound is obtained as an oil, MS (ES$^+$): 210 $(MH)^+$.

In addition, 6-fluoro-3-methyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester and 8-fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester can be isolated as byproducts.

Example 4: 8-Fluoro-isoquinoline-3-carboxylic acid {(R)-1-azabicyclo[2.2.2]oct-2-yl}-amide

The title compound is prepared according to Example 1 starting from 3(R)-aminoquinuclidine and 8-fluoro-isoquinoline-3-carboxylic acid. Further purification is achieved by chromatography on silica gel eluting with MeOtBu/EtOH/conc. aqu. NH_3 (80/18/2).

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.38 (1H, m), 1.63 (2H, dt), 1.78 (1H, m), 1.93 (1H, q), 2.64-2.81 (4H, m), 2.93 (1H, dt), 3.17 (1H, dt), 4.07 (1H, m), 7.63 (1H, dt), 7.90 (1H, dd), 8.09 (1H, d), 8.63 (1H, s), 8.79 (1H, d), 9.53 (1H, s).
MS (ES^+): 300 $(MH)^+$

The starting material can be prepared as follows:

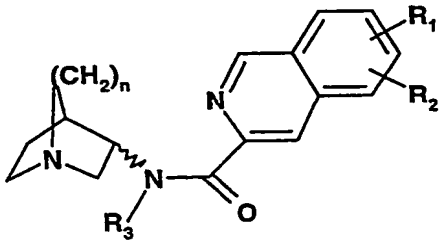
8-Fluoro-isoquinoline-3-carboxylic acid hydrochloride
The compound is prepared by oxidation of 8-fluoro-1,2,3,4-tetrahydro-isoquinoline -3-carboxylic acid methyl ester, followed by saponification according to the preparation of 6-fluoro-isoquinoline-3-carboxylic acid (Example 3).

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 7.68 (1H, dd), 7.92 (1H, dd), 8.09 (1H, d), 8.71 (1H, s), 9.57 (1H, s).
MS (ES^-) : 190 $(M-H)^-$

8-Fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester
The compound is obtained as a byproduct during the synthesis of 6-fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester (see Example 3).
MS (EI): 209 (M^+)

Claims:

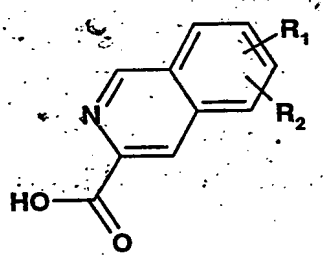
1. A compound of formula I



I

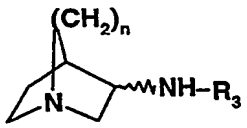
wherein R_1 and R_2, independently, are hydrogen, (C_{1-4})alkyl, halogen, hydroxy, (C_{1-4})alkoxy, di(C_{1-4})alkylamino, (C_{1-4})alkylthio, cyano or trifluoromethyl, R_3 is hydrogen or (C_{1-4})alkyl and n is 1 or 2, in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II



II

wherein R_1 and R_2 are as defined in claim 1, with a compound of formula III



III

wherein R_3 and n are as defined in claim 1, and recovering the resulting compound of formula I in free base or acid addition salt form.

3. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of psychotic and neurodegenerative disorders.

5. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of psychotic and neurodegenerative disorders.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of psychotic and neurodegenerative disorders.

8. A method for the treatment of psychotic and neurodegenerative disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

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